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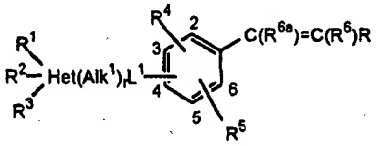

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(57) Abstract

Compounds of formula (1) are described in which Het is a heteroaromatic group, Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain and R is a carboxylic acid or a derivative thereof. The compounds are able to inhibit the binding of α_4 integrins to their ligands and are of use in the prophylaxis and treatment of immune or inflammatory disorders.

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CINNAMIC ACID DERIVATIVES AS CELL ADHESION MOLECULES

This invention relates to a series of cinnamic acid derivatives, to compositions containing them, to processes for their preparation, and to their use in medicine.

Over the last few years it has become increasingly clear that the physical interaction of inflammatory leukocytes with each other and other cells of the body plays an important role in regulating immune and inflammatory responses [Springer, T A. Nature, 346, 425, (1990); Springer, T. A. Cell 76, 301, (1994)]. Many of these interactions are mediated by specific cell surface molecules collectively referred to as cell adhesion molecules.

The adhesion molecules have been sub-divided into different groups on the basis of their structure. One family of adhesion molecules which is believed to play a particularly important role in regulating immune and inflammatory responses is the integrin family. This family of cell surface glycoproteins has a typical non-covalently linked heterodimer structure. At least 14 different integrin alpha chains and 8 different integrin beta chains have been identified [Sonnenberg, A. Current Topics in Microbiology and Immunology, 184, 7, (1993)]. The members of the family are typically named according to their heterodimer composition although trivial nomenclature is widespread in this field. Thus the integrin termed $\alpha 4\beta 1$ consists of the integrin alpha 4 chain associated with the integrin beta 1 chain, but is also widely referred to as Very Late Antigen 4 or VLA4. Not all of the potential pairings of integrin alpha and beta chains have yet been observed in nature and the integrin family has been subdivided into a number of subgroups based on the pairings that have been recognised [Sonnenberg, A. *ibid*].

The importance of cell adhesion molecules in human leukocyte function has been further highlighted by a genetic deficiency disease called Leukocyte Adhesion Deficiency (LAD) in which one of the families of leukocyte integrins is not expressed [Marlin, S. D. *et al* J. Exp. Med. 164, 855 (1986)]. Patients with this disease have a reduced ability to recruit

leukocytes to inflammatory sites and suffer recurrent infections which in extreme cases may be fatal.

The potential to modify adhesion molecule function in such a way as to beneficially modulate immune and inflammatory responses has been extensively investigated in animal models using specific monoclonal antibodies that block various functions of these molecules [e.g. Issekutz, T. B. J. Immunol. 3394, (1992); Li, Z. *et al* Am. J. Physiol. 263, L723, (1992); Binns, R. M. *et al* J. Immunol. 157, 4094, (1996)]. A number of monoclonal antibodies which block adhesion molecule function are currently being investigated for their therapeutic potential in human disease.

One particular integrin subgroup of interest involves the α4 chain which can pair with two different beta chains β1 and β7 [Sonnenberg, A. *ibid*]. The α4β1 pairing occurs on many circulating leukocytes (for example lymphocytes, monocytes and eosinophils) although it is absent or only present at low levels on circulating neutrophils. α4β1 binds to an adhesion molecule (Vascular Cell Adhesion Molecule-1 also known as VCAM-1) frequently up-regulated on endothelial cells at sites of inflammation [Osborne, L. Cell, 62, 3, (1990)]. The molecule has also been shown to bind to at least three sites in the matrix molecule fibronectin [Humphries, M. J. *et al*. Ciba Foundation Symposium, 189, 177, (1995)]. Based on data obtained with monoclonal antibodies in animal models it is believed that the interaction between α4β1 and ligands on other cells and the extracellular matrix plays an important role in leukocyte migration and activation [Yednock, T. A. *et al*, Nature, 356, 63, (1992); Podolsky, D. K. *et al*. J. Clin. Invest. 92, 373, (1993); Abraham, W. M. *et al*. J. Clin. Invest. 93, 776, (1994)].

The integrin generated by the pairing of α4 and β7 has been termed LPAM-1 [Holzmann, B and Weissman, I. EMBO J. 8, 1735, (1989)] and like α4β1, binds to VCAM-1 and fibronectin. In addition, α4β7 binds to an adhesion molecule believed to be involved in the homing of leukocytes to mucosal tissue termed MAdCAM-1 [Berlin, C. *et al*, Cell, 74, 185, (1993)]. The interaction between α4β7 and MAdCAM-1 may also be important at

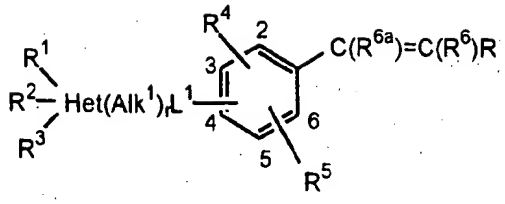
sites of inflammation outside of mucosal tissue [Yang, X-D. *et al*, PNAS, 91, 12604 (1994)].

Regions of the peptide sequence recognised by α4β1 and α4β7 when they bind to their ligands have been identified. α4β1 seems to recognise LDV, IDA or REDV peptide sequences in fibronectin and a QIDSP sequence in VCAM-1 [Humphries, M. J. *et al*, *ibid*] whilst α4β7 recognises a LDT sequence in MAdCAM-1 [Briskin, M. J. *et al*, J. Immunol. 156, 719, (1996)]. There have been several reports of inhibitors of these interactions being designed from modifications of these short peptide sequences [Cardarelli, P. M. *et al* J. Biol. Chem. 269, 18668, (1994); Shroff, H. N. Bioorganic. Med. Chem. Lett. 6, 2495, (1996); Vanderslice, P. J. Immunol. 158, 1710, (1997)]. It has also been reported that a short peptide sequence derived from the α4β1 binding site in fibronectin can inhibit a contact hypersensitivity reaction in a trinitrochlorobenzene sensitised mouse [Ferguson, T. A. *et al*, PNAS 88, 8072, (1991)].

Since the alpha 4 subgroup of integrins are predominantly expressed on leukocytes their inhibition can be expected to be beneficial in a number of immune or inflammatory disease states. However, because of the ubiquitous distribution and wide range of functions performed by other members of the integrin family it is very important to be able to identify selective inhibitors of the alpha 4 subgroup.

We have now found a group of compounds which are potent and selective inhibitors of α4 integrins. Members of the group are able to inhibit α4 integrins such as α4β1 and/or α4β7 at concentrations at which they generally have no or minimal inhibitory action on α integrins of other subgroups. The compounds are thus of use in medicine, for example in the prophylaxis and treatment of immune or inflammatory disorders as described hereinafter.

Thus according to one aspect of the invention we provide a compound of formula (1)



(1)

wherein

Het is a heteroaromatic group;

R^1, R^2 and R^3 which may be the same or different is each an atom or group $-L^2(Alk^2)_tL^3(R^7)_u$ in which L^2 and L^3 which may be the same or different is each a covalent bond or a linker atom or group, t is zero or the integer 1, u is an integer 1, 2 or 3, Alk^2 is an aliphatic or heteroaliphatic chain and R^7 is a hydrogen or halogen atom or a group selected from alkyl, $-OR^8$ [where R^8 is a hydrogen atom or an optionally substituted alkyl group], $-SR^8$, $-NR^8R^9$ [where R^9 is as just defined for R^8 and may be the same or different], $-NO_2$, -CN, $-CO_2R^8$, $-OCO_2R^8$, $-CONR^8R^9$, $-OCONR^8R^9$, $-CSNR^8R^9$, $-COR^8$, $-OCOR^8$, $-N(R^8)COR^9$, $-N(R^8)CSR^9$, $-SO_2N(R^8)(R^9)$, $-N(R^8)SO_2R^9$, $-N(R^8)CON(R^9)(R^{10})$, [where R^{10} is a hydrogen atom or an optionally substituted alkyl group] $-N(R^8)CSN(R^9)(R^{10})$ or $-N(R^8)SO_2N(R^9)(R^{10})$;

Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain;

L^1 is a covalent bond or a linker atom or group;

R^4 and R^5, which may be the same or different, is each a hydrogen or halogen atom or an alkyl, alkoxy, hydroxy or nitro group;

R^6 and R^{6a}, which may be the same or different, is each an atom or group $-L^2(Alk^2)_tL^3R^{11}$ in which L^2, L^3, Alk^2 and t are as previously defined and R^{11} is a hydrogen or halogen atom or an $-OR^8$, $-NR^8R^9$, $-NO_2$, -CN, $-CO_2R^8$, $-CONR^8R^9$, $-COR^8$, $-N(R^8)COR^9$, $-N(R^8)CSR^9$, $-SO_2N(R^8)(R^9)$, $-N(R^8)SO_2R^8$, $-N(R^8)CON(R^9)(R^{10})$, $-N(R^8)CSN(R^9)(R^{10})$, $-N(R^8)SO_2N(R^9)(R^{10})$, or an optionally substituted aliphatic, heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group;

r is zero or the integer 1;

R is a carboxylic acid ($-CO_2H$) or a derivative thereof;

and the salts, solvates, hydrates and N-oxides thereof.

It will be appreciated that compounds of formula (1) exist as geometric isomers (E or Z isomers). The compounds may also have one or more chiral centres, and exist as enantiomers or diastereomers. The invention is to be understood to extend to all such geometric isomers, enantiomers, diasteromers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise.

In the compounds of formula (1), derivatives of the carboxylic acid group R include carboxylic acid esters and amides. Particular esters and amides include $-CO_2Alk^5$ and $-CONR^8R^9$ groups as described herein.

In general, the substituents R^1, R^2 and R^3 in compounds of the invention may be positioned on any available carbon atom, or, when present, nitrogen atom in the heteroaromatic group represented by Het.

When in the compounds of formula (1) L^1, L^2 and/or L^3 is present as a linker atom or group it may be any divalent linking atom or group. Particular examples include -O- or -S- atoms or -C(O)-, -C(O)O-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^{12})-$ [where R^{12} is a hydrogen atom or an optionally substituted alkyl group], $-CON(R^{12})-$, $-OC(O)N(R^{12})-$, $-CSN(R^{12})-$, $-N(R^{12})CO-$, $-N(R^{12})C(O)O-$, $-N(R^{12})CS-$, $-S(O)_2N(R^{12})-$, $-N(R^{12})S(O)_2-$, $-N(R^{12})CON(R^{12})-$, $-N(R^{12})CSN(R^{12})-$, or $-N(R^{12})SO_2N(R^{12})-$ groups. Where the linker group contains two R^{12} substituents, these may be the same or different.

When R^4, R^5, R^7, R^8, R^9, R^{10} and/or R^{12} in the compounds of formula (1) is an alkyl group it may be a straight or branched C_{1-6}alkyl group, e.g. a C_{1-3}alkyl group such as a methyl or ethyl group. Optional substituents which may be present on such groups include for example one, two or three substituents which may be the same or different selected from halogen atoms, for example fluorine, chlorine, bromine or iodine atoms, or hydroxy or C_{1-6}alkoxy e.g. methoxy or ethoxy groups.

Alkoxy groups represented by R^4 and/or R^5 in compounds of formula (1) include C_{1-6}alkoxy groups such as methoxy or ethoxy groups. Halogen

atoms represented by R^4 and/or R^5 include fluorine, chlorine, bromine, or iodine atoms.

When Alk^1 in compounds of formula (1) is an optionally substituted aliphatic chain it may be an optionally substituted C_{1-10} aliphatic chain. Particular examples include optionally substituted straight or branched chain C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl chains.

Heteroaliphatic chains represented by Alk^1 include the aliphatic chains just described but with each chain additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L^4 where L^4 is as defined above for L^1 when L^1 is a linker atom or group. Each L^4 atom or group may interrupt the aliphatic chain, or may be positioned at its terminal carbon atom to connect the chain to an adjoining atom or group.

Particular examples of aliphatic chains represented by Alk^1 include optionally substituted $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-(CH_2)_2CH_2-$, $-CH(CH_3)CH_2-$, $-(CH_2)_3CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-C(CH_3)_2CH_2-$, $-(CH_2)_4CH_2-$, $-(CH_2)_5CH_2-$, $-CHCH-$, $-CHCHCH_2-$, $-CH_2CHCH-$, $-CHCHCH_2CH_2-$, $-CH_2CHCHCH_2-$, $-(CH_2)_2CHCH-$, $-CC-$, $-CCCH_2-$, $-CH_2CC-$, $-CCCH_2CH_2-$, $-CH_2CCCH_2-$, or $-(CH_2)_2CC-$ chains. Where appropriate each of said chains may be optionally interrupted by one or two atoms and/or groups L^4 to form an optionally substituted heteroaliphatic chain. Particular examples include optionally substituted $-L^4CH_2-$, $-CH_2L^4CH_2-$, $-L^4(CH_2)_2-$, $-CH_2L^4(CH_2)_2-$, $-(CH_2)_2L^4CH_2-$, $-L^4(CH_2)_3-$ and $-(CH_2)_2L^4(CH_2)_2-$ chains. The optional substituents which may be present on aliphatic or heteroaliphatic chains represented by Alk^1 include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkoxy, e.g. methoxy or ethoxy, thiol, C_{1-6}alkylthio e.g. methylthio or ethylthio, amino or substituted amino groups. Substituted amino groups include $-NHR^{13}$ and $-N(R^{13})_2$ groups where R^{13} is an optionally substituted straight or branched alkyl group as defined above for R^{12}. Where two R^{13} groups are present these may be the same or different.

Particular examples of substituted chains represented by Alk^1 include those specific chains just described substituted by one, two, or three halogen atoms such as fluorine atoms, for example chains of the type $-CH(CF_3)-$, $-C(CF_3)_2-$ $-CH_2CH(CF_3)-$, $-CH_2C(CF_3)_2-$, $-CH(CF_3)-$ and $-C(CF_3)_2CH_2$.

When Alk^2 is present in the compounds of formulae (1) or (1a) as an aliphatic or heteroaliphatic chain it may be for example any of the above-mentioned C_{1-10}aliphatic or heteroaliphatic chains described for Alk^1.

Halogen atoms represented by R^7 and/or R^{11} include fluorine, chlorine, bromine, or iodine atoms.

When R^{11} is present in compounds of formula (1) as an optionally substituted aliphatic or heteroaliphatic group it may be an aliphatic or heteroaliphatic group equivalent to the aliphatic or heteroaliphatic chain just described for Alk^1. Each aliphatic or heteroaliphatic group may be optionally substituted by one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl, C_{1-6}alkoxy, e.g. methoxy or ethoxy, thiol, C_{1-6}alkylthio e.g. methylthio or ethylthio, $-NH_2$ or substituted amino such as $-NHR^{13}$ or $-N(R^{13})_2$ as described above.

Optionally substituted cycloaliphatic groups represented by R^{11} include optionally substituted C_{3-10} cycloaliphatic groups. Particular examples include optionally substituted C_{3-10}cycloalkyl, e.g. C_{3-7}cycloalkyl or C_{3-10} cycloalkenyl e.g. C_{3-7}cycloalkenyl groups.

Optionally substituted heterocycloaliphatic groups represented by R^{11} include the optionally substituted cycloaliphatic groups just described for R^{11} but with each group additionally containing one, two, three or four heteroatoms or heteroatom-containing groups L^4 where L^4 is as defined above.

Particular examples of R^{11} cycloaliphatic and heterocycloaliphatic groups include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, tetrahydrofuranyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, thiazolinyl, thiazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, piperidinone, 1,4-dioxanyl, morpholinyl, morpholinone, 1,4-dithianyl, thiomorpholinyl, piperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4-oxazinyl, isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5-oxadiazinyl groups.

The optional substituents which may be present on the R^{11} cycloaliphatic, or heterocycloaliphatic groups include one, two, three or more substituents each represented by R^{14} in which R^{14} is a halogen atom, e.g. a fluorine, chlorine, bromine or iodine atom, or a C_{1-6}alkoxy, e.g. methoxy or ethoxy, thiol, C_{1-6}alkylthio e.g. methylthio or ethylthio amino or substituted amino group, e.g. a $-NHR^{13}$ or $-N(R^{13})_2$ group as described above. Additionally, when R^{11} is a heterocycloaliphatic group containing one or more nitrogen atoms each nitrogen atom may be optionally substituted by a group $-(L^5)_p(Alk^3)_qR^{15}$ in which L^5 is $-C(O)-$, $-C(O)O-$, $-C(S)-$, $-S(O)_2-$, $-CON(R^{12})-$, $-CSN(R^{12})-$, $-SON(R^{12})-$ or $SO_2N(R^{12})-$; p is zero or an integer 1; Alk^3 is an optionally substituted aliphatic or heteroaliphatic chain; q is zero or an integer 1; and R^{15} is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group.

Optionally substituted aliphatic or heteroaliphatic chains represented by Alk^3 include those chains described above for Alk^1.

Optionally substituted cycloaliphatic or heterocycloaliphatic groups represented by R^{15} include those groups just described for R^{11}. Optional substituents which may be present on these groups include one, two or three R^{14} substituents as just described.

Optionally substituted polycycloaliphatic groups represented by R^{15} include optionally substituted C_{7-10}bi- or tricycloalkyl or C_{7-10}bi- or tricycoalkenyl groups, for example norbornyl, norbornenyl or adamantyl groups. Polyheterocycloaliphatic groups include the polycycloalkyl groups just mentioned but with each group additionally containing one, two, three or four atoms or groups selected from those atoms and groups L^4 described above. Optional substituents which may be present on the polycycloaliphatic or polyheterocycloaliphatic groups include those just described for R^{15} cycloaliphatic groups.

Optionally substituted aromatic or heteroaromatic groups represented by R^{15} included those aromatic and heteroaromatic groups generally and specifically described below for the group R^{11}.

Optionally substituted aromatic groups represented by the group R^{11} in compounds of the invention include for example monocyclic or bicyclic fused ring C_{6-12} aromatic groups, such as phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups, optionally substituted by one, two, three or more R^{16} atoms or groups as defined below.

Heteroaromatic groups represented by the group Het or R^{11} in the compounds of formula (1) include for example C_{1-9} heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example nine- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups of these types include pyrrolyl, furyl, thienyl, imidazolyl, N-C_{1-6}alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,

1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, benzothienyl, benzotriazolyl, indolyl, isoindolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]-pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, and imidyl, e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

Optional substituents which may be present on the aromatic or heteroaromatic groups represented by R^{11} include one, two, three or more substituents, each selected from an atom or group R^{17} in which R^{17} is $-R^{17a}$ or $-Alk^4(R^{17a})_m$, where R^{17a} is a halogen atom, or an amino ($-NH_2$), substituted amino, nitro, cyano, amidino, hydroxyl (-OH), substituted hydroxyl, formyl, carboxyl ($-CO_2H$), esterified carboxyl, thiol (-SH), substituted thiol, $-COR^{18}$ [where R^{18} is an $-Alk^3(R^{17a})_m$, aryl or heteroaryl group], $-CSR^{18}$, $-SO_3H$, $-SO_2R^{18}$ $-SO_2NH_2$, $-SO_2NHR^{18}$ $SO_2N(R^{18})_2$, $-CONH_2$, $-CSNH_2$, $-CONHR^{18}$, $-CSNHR^{18}$, $-CON[R^{18}]_2$, $-CSN(R^{18})_2$, $-N(R^{12})SO_2R^{18}$, $-N(SO_2R^{18})_2$, $-NH(R^{12})SO_2NH_2$, $-N(R^{12})SO_2NHR^{18}$, $-N(R^{12})SO_2N(R^{18})_2$, $-N(R^{12})COR^{18}$, $-N(R^{12})CON(R^{18})_2$, $-N(R^{12})CSN(R^{18})_2$, $-N(R^{12})CSR^{18}$, $-N(R^{12})C(O)OR^{18}$, $-SO_2NHet^1$ [where $-NHet^1$ is an optionally substituted C_{5-7}cyclicamino group optionally containing one or more other -O- or -S- atoms or $-N(R^{12})$-, -C(O)- or -C(S)- groups], $-CONHet^1$, $-CSNHet^1$, $-N(R^{12})SO_2NHet^1$, $-N(R^{12})CONHet^1$, $-N(R^{12})CSNHet^1$, $-SO_2N(R^{12})Het^2$ [where Het^2 is an optionally substituted monocyclic C_{5-7}carbocyclic group optionally containing one or more -O- or -S- atoms or $-N(R^{12})$-, -C(O)- or -C(S)- groups], $-CON(R^{12})Het^2$, $-CSN(R^{12})Het^2$, $-N(R^{12})CON(R^{12})Het^2$,$-N(R^{12})CSN(R^{12})Het^2$, aryl or heteroaryl group; Alk^4 is a straight or branched C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or $-S(O)_n$ [where n is an integer 1 or 2] or $-N(R^{19})$- groups [where R^{19} is a hydrogen atom or C_{1-6}alkyl, e.g. methyl or ethyl group]; and m is zero or an integer 1, 2 or 3. It will be appreciated that when two R^{12} or R^{18} groups are present in one of the above substituents, the R^{12} or R^{18} groups may be the same or different.

When in the group -$Alk^4(R^{17a})_m$ m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{17a} may be present on any suitable carbon atom in -Alk^4. Where more than one R^{17a} substituent is present these may be the same or different and may be present on the same or different atom in -Alk^4. Clearly, when m is zero and no substituent R^{17a} is present the alkylene, alkenylene or alkynylene chain represented by Alk^4 becomes an alkyl, alkenyl or alkynyl group.

When R^{17a} is a substituted amino group it may be for example a group -NHR^{18} [where R^{18} is as defined above] or a group -$N(R^{18})_2$ wherein each R^{18} group is the same or different.

When R^{17a} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R^{17a} is a substituted hydroxyl or substituted thiol group it may be for example a group -OR^{18} or a -SR^{18} or -$SC(=NH)NH_2$ group respectively.

Esterified carboxyl groups represented by the group R^{17a} include groups of formula -CO_2Alk^5 wherein Alk^5 is a straight or branched, optionally substituted C_{1-8}alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a $C_{6-12}arylC_{1-8}$alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12}aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a $C_{6-12}aryloxyC_{1-8}$alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyl-oxymethyl, or 2-naphthyloxymethyl group; an optionally substituted $C_{1-8}alkanoyloxyC_{1-8}$alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a $C_{6-12}aroyloxyC_{1-8}$alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk^5 group include R^{17a} substituents described above.

When Alk^4 is present in or as a substituent it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-

butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, -$S(O)_2$- or -$N(R^{12})$- groups.

Aryl or heteroaryl groups represented by the groups R^{17a} or R^{18} include mono- or bicyclic optionally substituted C_{6-12} aromatic or C_{1-9} heteroaromatic groups as described above for the group R^{11}. The aromatic and heteroaromatic groups may be attached to the remainder of the compound of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

When -$NHet^1$ or -Het^2 forms part of a substituent R^{17} each may be for example an optionally substituted pyrrolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl or thiazolidinyl group. Additionally Het^2 may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on -$NHet^1$ or -Het^2 include those R^7 substituents described above.

Particularly useful atoms or groups represented by R^{17} include fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrrolyl, furyl, thiazolyl, or thienyl, C_{1-6}alkylamino, e.g. methylamino or ethylamino, C_{1-6}hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC_{1-6}alkyl, e.g. carboxyethyl, C_{1-6}alkylthio e.g. methylthio or ethylthio, carboxyC_{1-6}alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C_{1-6}alkoxy, e.g. methoxy or ethoxy, hydroxyC_{1-6}alkoxy, e.g. 2-hydroxyethoxy, optionally substituted phenoxy, pyridyloxy, thiazolyoxy, phenylthio or pyridylthio, C_{5-7}cycloalkoxy, e.g. cyclopentyloxy, haloC_{1-6}alkyl, e.g. trifluoromethyl, haloC_{1-6}alkoxy, e.g. trifluoromethoxy, C_{1-6}alkylamino, e.g. methylamino or ethylamino, amino (-NH_2), aminoC_{1-6}alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, C_{1-6}alkylaminoC_{1-6}alkyl, e.g. ethylaminoethyl, C_{1-6}dialkylaminoC_{1-6}alkyl, e.g. diethylaminoethyl, aminoC_{1-6}alkoxy, e.g. aminoethoxy, C_{1-6}alkylaminoC_{1-6}alkoxy, e.g. methylaminoethoxy, C_{1-6}dialkylaminoC_{1-6}alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy,

isopropylaminoethoxy, or dimethylaminopropoxy, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO_2H), -CO_2Alk^5 [where Alk^5 is as defined above], C_{1-6} alkanoyl e.g. acetyl, optionally substituted benzoyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, -SC(=NH)NH_2, sulphonyl (-SO_3H), C_{1-6}alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl (-SO_2NH_2), C_{1-6}alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6}dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido (-$CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6}dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC_{1-6}alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C_{1-6}dialkylaminoC_{1-6}alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C_{1-6}alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C_{1-6}dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C_{1-6}alkylaminocabonylC_{1-6}alkylamino, e.g. methylaminocarbonylmethylamino, aminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C_{1-6}dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylC_{1-6}alkylamino, e.g. ethylaminothiocarbonylmethylamino, -CONHC(=NH)NH_2, C_{1-6}alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C_{1-6}dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino (-$NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, e.g. methylaminosulphonyl-amino or ethylaminosulphonylamino, C_{1-6}dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, optionally substituted morpholinesulphonylamino or morpholinesulphonylC_{1-6}alkylamino, optionally substituted phenylaminosulphonylamino, C_{1-6}alkanoylamino, e.g. acetylamino, aminoC_{1-6}alkanoylamino e.g. aminoacetylamino, C_{1-6}dialkylaminoC_{1-6}alkanoylamino, e.g. dimethylaminoacetylamino, C_{1-6}alkanoylaminoC_{1-6}alkyl, e.g. acetylaminomethyl, C_{1-6}alkanoylaminoC_{1-6}alkylamino, e.g. acetamidoethylamino, C_{1-6}alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino or

optionally substituted benzyloxy, pyridylmethoxy, thiazolylmethoxy, benzyloxycarbonylamino, benzyloxycarbonylaminoC_{1-6}alkyl e.g. benzyloxycarbonylaminoethyl, benzothio, pyridylmethylthio or thiazolylmethylthio groups.

Where desired, two R^{17} substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{1-6}alkylenedioxy group such as methylenedioxy or ethylenedioxy.

It will be appreciated that where two or more R^{17} substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position in the aromatic or heteroaromatic group represented by R^{11}.

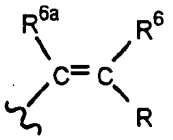
The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isothionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

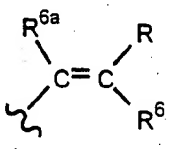
Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

As noted above, the compounds of formula (1) may exist as geometric isomers. Thus, for example, one set of isomeric pairs of compounds of formula (1) is that wherein the R^6 and R^{6a}-containing groups are in a cis:



(A)

or trans relationship:



(B)

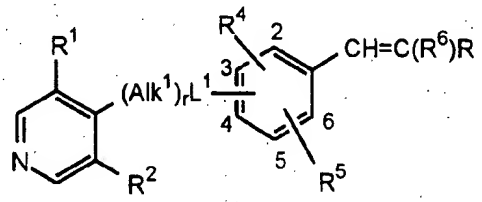
Although as explained previously the invention extends and relates to all geometric isomers of compounds of formla (1) certain of these isomers have particularly advantageous pharmacokinetic properties which makes them especially suitable for use in medicine. Thus, generally R^6 and R^{6a} are preferably in a trans relationship to each other [(B) above] in the compounds of formula (1).

In the compounds according to the invention the group Het is preferably a monocyclic heteroaromatic group. Particularly useful groups of this type are five- or six-membered heteroaromatic groups as described previously for Het, especially five- or six-membered heteroaromatic groups containing one or two heteroatoms selected from oxygen, sulphur or nitrogen atoms. Nitrogen-containing groups are especially useful, particularly pyridyl or pyrimidinyl groups.

In general in compounds of the invention each of R^1, R^2 and R^3 is preferably a hydrogen atom or an optionally substituted alkyl, $-OR^8$, $-SR^8$, $-NR^8R^9$, $-COR^8$, $-CO_2R^8$, $-NO_2$ or -CN group as defined herein.

In one preferred grop of comppounds of formula (1) R^{6a} is a hydrogen atom.

A particularly useful group of compounds according to the invention has the formula (2):



(2)

wherein R^1 and R^2, which may be the same or different is each an atom or group $-L^2(Alk^2)_tL^3(R^7)_u$ in which L^2, Alk^2, t, L^3, R^7 and u are as defined for formula (1) provided that R^1 and R^2 are not both hydrogen atoms;
Alk^1, r, L^1, R^4, R^5 and R are as defined for formula (1);
R^6 is an atom or group $-L^2(Alk^2)_tL^3R^{11}$ in which L^2, L^3, Alk^2 and t are as previously defined and R^{11} is a hydrogen or halogen atom or an $-OR^8$, $-NR^8R^9$, $-NO_2$, $-CN$, $-CO_2R^8$, $-CONR^8R^9$, $-COR^8$, $-N(R^8)COR^9$, $-N(R^8)CSR^9$, $-SO_2N(R^8)(R^9)$, $-N(R^8)SO_2R^8$, $-N(R^8)CON(R^9)(R^{10})$, $-N(R^8)CSN(R^9)(R^{10})$, $-N(R^8)SO_2N(R^9)(R^{10})$, or an optionally substituted aliphatic, heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group;
and the salts, solvates, hydrates and N-oxides thereof.

In the compounds of formula (2) the R^6 and pyridyl-containing substituents preferably have a cis relationship as shown in (B) above.

R^1 and R^2 in compounds of formula (2) is each preferably as described above other than a hydrogen atom. Particularly useful R^1 and R^2 substituents in compounds of the invention include halogen atoms, especially fluorine or chlorine atoms, methyl, ethyl, methoxy, ethoxy, $-CF_3$, $-OH$, $-CN$, $-NO_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-COCH_3$, $-SCH_3$, $-CO_2H$ or $-CO_2CH_3$ groups.

R in the compounds of formulae (1) and (2) is preferably a $-CO_2H$ group.

When present, the aliphatic chain represented by Alk^1 in compounds of formulae (1) and (2) is preferably a $-CH_2-$ chain.

In general in compounds of formulae (1) and (2) $-(Alk^1)_rL^1-$ is preferably $-CH_2O-$ or $-CON(R^{12})-$, and is especially a -CONH- group. The $-(Alk^1)_rL^1-$ group is preferably attached to the 4-position of the phenyl ring containing the R^4 and R^5 substituents.

Particularly useful classes of compounds according to the invention are those wherein R^6 is a $-L^2R^{11}$ or $-L^2Alk^2R^{11}$ atom or group. In these classes, L^2 when present as a linker atom or group may especially be a -NHCO-, -NHCS- or $-NHSO_2-$ group. Alk^2 when present may especially be a C_{1-4}alkylene chain. R^{11} may especially be a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group as defined herein. Particularly useful R^{11} groups include optionally substitued C_{5-7}cycloaliphatic, especially optionally substituted pyrrolidinyl, optionally substituted C_{5-7}heterocycloaliphatic, especially optionally substituted pyrrolidinyl or thiazolidinyl, optionally substituted phenyl and optionally substituted C_{5-7}heteroaromatic, especially optionally substituted pyridinyl groups. Optional substituents on these groups include in particular R^{17} atoms or groups where the group is an aromatic or heteroaromatic group and $-(L^5)_p(Alk^3)_qR^{15}$ groups as described earlier where the group is a nitrogen-containing heterocycloaliphatic group such as a pyrrolidinyl or thiazolidinyl group. Particularly useful $-(L^5)_p(Alk^3)_qR^{15}$ groups include $-L^5CH_2R^{15}$ groups in which R^{15} is a hydrogen atom or an optionally substituted aromatic, particularly optionally substituted phenyl, or optionally substituted heteroaromatic, particularly optionally substituted pyridyl group as defined herein. In these groups L^5 may be as defined above, and is especially a -C(O)- group.

Particularly useful compounds according to the invention include:
N-Acetyl-*D*-thioproline-4-[(3,5-dichloroisonicotinoyl)amino]-*Z*-didehydrophenylalanine;
N-Acetyl-*D*-thioproline-4-[(3,5-dichloroisonicotinoyl)amino]-*E*-didehydrophenylalanine;

N-Trimethylacetyl-4-[(3,5-dichloroisonicotinoyl)amino]-*Z*-didehydrophanylalanine;
N-Trimethylacetyl-4-[(3,5-dichloroisonicotinoyl)amino]-*E*-didehydrophenylalanine;
N-(2-Chloronicotinoyl)-4-[(3,5-dichloroisonicotinoyl)amino]-*Z*-didehydrophenylalanine;
(*Z*)-3-{4-[(3,5-Dichloro-4-pyridinyl)methoxy]phenyl}-2-[(2,6-dimethoxybenzoyl)amino]-2-propenoic acid;
N-(2-Chloronicotinoyl)-4-[(3,5-dichloroisonicotinoyl)amino]-*E*-didehydrophenylalanine;
and the salts, solvates, hydrates and N-oxides thereof.

Compounds according to the invention are potent and selective inhibitors of $\alpha 4$ integrins. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter. In particular compounds of the invention, such as the compounds of formula (1a) herein, are advantageously selective $\alpha 4\beta_1$ inhibitors.

The compounds are of use in modulating cell adhesion and in particular are of use in the prophylaxis and treatment of diseases or disorders involving inflammation in which the extravasation of leukocytes plays a role and the invention extends to such a use and to the use of the compounds for the manufacture of a medicament for treating such diseases or disorders.

Diseases or disorders of this type include inflammatory arthritis such as rheumatoid arthritis vasculitis or polydermatomyositis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses such as psoriasis or dermatitis, asthma and inflammatory bowel disease.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively,

the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

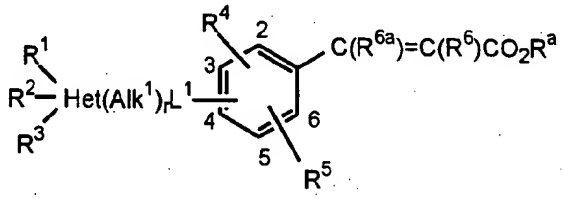
The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols R^1-R^6 and R^{6a}, L^1, Alk^1 and r when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it

may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups. For convenience the processes described below all refer to a preparation of a compound of formula (1) but clearly the description applies equally to the preparation of compounds of formulae (1a) and (2).

Thus according to a further aspect of the invention, a compound of formula (1) in which R is a $-CO_2H$ group may be obtained by hydrolysis of an ester of formula (3):

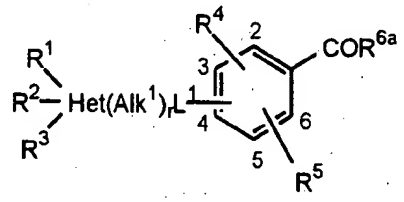


(3)

where R^a is an alkyl group, for example a C_{1-6}alkyl group as described above.

The hydrolysis may be performed using either an acid or a base depending on the nature of R^a, for example an organic acid such as trifluoracetic acid or an inorganic base such as lithium or potassium hydroxide optionally in an aqueous organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran or dioxane or an alcohol, e.g. methanol at around ambient temperature. Where desired, mixtures of such solvents may be used.

Esters of formula (3) and, in general, esters of formula (1) in which R is a $-CO_2$ Alk^5 group may be prepared by reaction of an aldehyde or ketone of formula (4):



(4)

with a phosphonate $(Alk^6O)_2P(O)CH(R^6)CO_2Alk^5$, where Alk^6 is a C_{1-6}alkyl group optionally substituted by one or more fluorine atoms, in the presence of a base.

Suitable bases include organometallic bases, for example an organolithium compound such as n-butyllithium or lithium diisopropylamide, hydrides such as sodium or potassium hydride, alkoxides, such as sodium alkoxides, e.g. sodium methoxide, and cyclic amines, for example 1,8-diazabicyclo[5.4.0]undec-7-ene.

The reaction may be performed in a suitable solvent, for example a polar aprotic solvent such as an amide, e.g. N,N-dimethylformamide; or a non-polar solvent such as an ether, e.g. a cyclic ether such as tetrahydrofuran or a halogenated hydrocarbon, e.g. dichloromethane. Preferably the reaction is carried out at a low temperature for example from around -78°C to around ambient temperature.

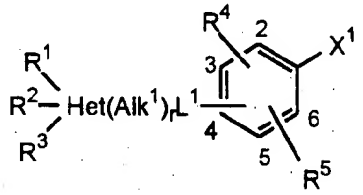
Intermediate phosphonates of formula $(Alk^6O)_2P(O)CH(R^6)CO_2Alk^5$ are either known compounds or may be obtained by reaction of a halide $HalCH(R^6)CO_2Alk^5$ [where Hal is a halogen atom such as a chlorine or bromine atom] with a phosphite $P(OAlk^6)_3$. The halides $HalCH(R^6)CO_2Alk^5$ are either known compounds or may be prepared by manipulation of known compounds by the standard substitution, oxidation, reduction and/or cleavage reactions described hereinafter. In general the reaction with the phosphite $P(OAlk^6)_3$ may be carried out at any stage in the synthesis of the desired phosphonate $(Alk^6O)_2P(O)CH(R^6)CO_2Alk^5$.

Intermediate aldehydes of formula (4) are either known compounds or may be prepared by simple chemical manipulation of known compounds.

Thus, for example, the aldehydes [where R^{6a} is a hydrogen atom] may be obtained by oxidation of the corresponding alcohols [in which $-COR^{6a}$ is replaced by a -CHOH group] using an oxidising agent such as manganese (IV) oxide in a solvent such as dichloromethane.

Intermediate ketones of formula (4) [where R^{6a} is other than a hydrogen atom] may also be obtained by oxidation of the corresponding alcohol of formula (4), using for example manganese (IV) oxide in a solvent such as dichlromethane, or by reaction of a corresponding halide [in which $-COR^{6a}$ has been replaced by a halogen atom such as a bromine or chlorine atom] by halogen-metal exchange with a base such as n-butyllithium followed by reaction wtih a nitrile $R^{6a}CN$, an acid chloride $R^{6a}COCl$ or an ester $R^{6a}CO_2R^a$, in a solvent such as tetrahydrofuran, at a low temperature e.g. around -70°C and subsequent treatment with an acid such as hydrochloric acid at around ambient temperature.

In another process, esters or amides of formula (1), for example where R is a carboxylic acid ester or amide, and in which R^6 or R^{6a} is a hydrogen atom, may be prepared by coupling an organpalladium compound derived from an intermediate of formula (5):



(5)

[in which X^1 is a halogen atom such as an iodine atom or is a trifluoromethylsulphonyloxy group] and a palladium salt with an ester or amide $R^{6a}CHCHR$ or $CH_2C(R^6)R$ where R is as just defined in the presence of a base.

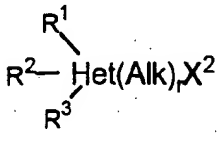
Suitable palladium salts include palladium acetate or palladium chloride. Where palladium acetate is used the reaction for example may be carried out under phase-transfer conditions in the presence of tetra-n-butylammonium bromide and an alkali-metal base such as sodium bicarbonate in dimethylformamide. In another example, the reaction may be performed using palladium acetate or palladium chloride and a phosphine, for example a triarylphosphine such as triphenylphosphine, and a base such as triethylamine, at for example an elevated temperature and pressure.

Where desired, the starting materials in the above general coupling reaction may be varied. The reaction may thus be performed using an ester or amide of formula (1) in which R is a carboxylic acid ester or amide and R^6 and R^{6a} is each a hydrogen atom with a reagent $R^{6b}X^1$ in which R^{6b} is an aromatic or heteroaromatic group and X^1 is as defined above. Similarly the reaction may be used to generate intermediates to the final compounds described herein, for example intermediate esters of formula (3) by using the appropriate alkene ester and a reagent $R^{6b}X^1$.

Where necessary, the intermediate aldehydes and ketones of formula (4) and the corresponding alcohols and halides described above, as well as the intermediates of formula (5) and the esters or amides $R^{6a}CHCHR$ or $CH_2C(R^6)R$ may be obtained from simpler aromatic or heteroaromatic compounds by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to modify the compounds of formula (1) and the esters (3) where appropriate functional groups exist in these compounds and to generate suitable phosphonates $(Alk^6O)_2P(O)CH(R^6)CO_2Alk^5$ for example to obtain desired groups $-CH(R^6)CO_2Alk^5$ therein.

Thus compounds of the invention and intermediates thereto may be prepared by alkylation, arylation or heteroarylation. For example,

compounds containing a $-L^1H$, $-L^2H$, or $-L^3H$ group (where L^1, L^2 and L^3 (is each a linker atom or group) may be treated with an alkylating agent:



, $R^{11}L^3(Alk^2)_tX^2$ or $R^{11}X^2$ in which X^2 is a leaving atom or group such as a halogen atom, e.g. a fluorine, bromine, iodine or chlorine atom or a sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy, e.g. p-toluenesulphonyloxy group.

The reaction may be carried out in the presence of a base such as a carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran.

In another example, compounds containing a $-L^1H$, $-L^2H$ or $-L^3H$ group as defined above may be functionalised by acylation or thioacylation, for example by reaction with one of the alkylating agents just described but in which X^2 is replaced by a $-C(O)X^3$, $C(S)X^3$, $-N(R^8)COX^3$ or $-N(R^8)C(S)X^3$ group in which X^3 is a leaving atom or group as described for X^2. The reaction may be performed in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide, at for example ambient temperature. Alternatively, the acylation or thioacylation may be carried out under the same conditions with an acid or thioacid (for example one of the alkylating agents described above in which X^2 is replaced by a $-CO_2H$ or -COSH group) in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole.

Alternatively the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to the desired acylation reaction

In a further example compounds may be obtained by sulphonylation of a compound containing an -OH group by reaction with one of the above alkylating agents but in which X^2 is replaced by a -S(O)Hal or -SO_2Hal group in which Hal is a halogen atom such as chlorine atom] in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature.

In another example, compounds containing a -L^1H, -L^2H or -L^3H group as defined above may be coupled with one of the alkylation agents just described but in which X is preplaced by an -OH group in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl, diisopropyl- or dimethylazodicarboxylate.

In a further example, ester groups -CO_2R^8 or -CO_2Alk^5 in the compounds may be converted to the corresponding acid [-CO_2H] by acid- or base-catalysed hydrolysis depending on the nature of the groups R^8 or Alk^5. Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol.

In a second example, -OR^8 or -OR^{18} groups [where R^8 or R^{18} each represents an alkyl group such as methyl group] in compounds of formula (1) may be cleaved to the corresponding alcohol -OH by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C.

Alcohol [-OH] groups may also be obtained by hydrogenation of a corresponding -OCH_2R^{18} group (where R^{18} is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or

hydrogen, from around ambient to the reflux temperature. In another example, -OH groups may be generated from the corresponding ester [$-CO_2Alk^5$ or CO_2R^8] or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

In another example, alcohol -OH groups in the compounds may be converted to a corresponding $-OR^8$ group by coupling with a reagent R^8OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate.

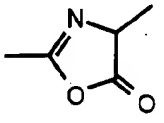
Aminosulphonylamino [$-NHSO_2NH_2$] groups in the compounds may be obtained, in another example, by reaction of a corresponding amine [$-NH_2$] with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

In a further example amine ($-NH_2$) groups may be alkylated using a reductive alkylation process employing an aldehyde and a borohydride, for example sodium triacetoxyborohyride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature.

In a further example, amine [$-NH_2$] groups in compounds of formula (1) may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [$-NO_2$] group may be reduced to an amine [$-NH_2$], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal,

e.g. tin or iron, in the presence of an acid such as hydrochloric acid in a solvent such as ethanol at an elevated temperature

Reduction, for example using a metal and reaction conditions as just described, may also be used to obtain a compound in which L^2 is a -NHCO- group from the corresponding oxazolone in which L is  . The oxazolone may be prepared by reaction of an appropriate amino acid or a reactive derivative thereof and a ketone in the presence of a catalyst, for example a lead salt such as lead acetale, in a solvent such as tetrahydrofuran at an elevated temperature.

Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile; a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile.

In a further example, compounds in which R^{6a} is an aromatic group may be prepared by reaction of a corresponding compound in which R^{6a} is a halogen atom such as a bromine atom with a boronic acid $R^{6a}B(OH)_2$ [where R^{6a} is an aromatic group] in the presence of a complex metal catalyst. Suitable catalysts include heavy metal catalysts, for example palladium catalysts, such as tetrakis(triphenylphosphine)palladium. The reaction may be performed in an inert organic solvent, for example an ether such as dimethoxyethane or dioxane, in the presence of a base, e.g. an alkali carbonate such as sodium carbonate, at an elevated temperature, e.g. the reflux temperature.

In another example, sulphur atoms in the compounds, for example when present in a linker group L^1, L^2 or L^3 may be oxidised to the corresponding sulphoxide or sulphone using an oxidising agent such as a peroxy acid,

e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base in a suit able solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

Chromatography, recrystalliation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

The following Examples illustrate the invention. All temperatures are in °C. The following abbreviations are used:

DMF - dimethylformamide; DMSO - dimethylsulphoxide;
HOBT - 1-hydroxybenzotriazole; THF - tetrahydrofuran;
NMM - N-methylmorpholine; EtOAc - ethyl acetate;
MeOH - methanol; LDA - lithium diisopropylamide
Ar - aryl; py - pyridine;
Me - methyl; Bu - butyl;
DBU - 1,8-diazabicyclo[5.4.0]undec-7-ene; DME - dimethoxyethane

All NMR's were obtained at 300mHz.

INTERMEDATE 1

N-Acetyl-*D*-thioproline-α-phosphonoglycine trimethyl ester

A mixture of N-(benzyloxycarbonyl)-α-phosphonoglycine trimethyl ester (5g, 15mmol) and palladium on charcoal (10%Pd, 500mg) in methanol (50ml) was stirred under a hydrogen atmosphere (balloon) at room temperature for 4h. The mixture was filtered through Celite® and the filtrate evaporated under reduced pressure to give the corresponding amine. A mixture of this amine, N-acetyl thioproline (2.63g, 15mmol), HOBT (2.23g, 16.5mmol) and NMM (1.81ml, 16.5mmol) was dissolved in CH_2Cl_2 (75ml). EDC (3.17g, 16.5mmol) was added and the mixture stirred overnight at room temperature. It was then diluted with CH_2Cl_2 (200ml) and washed with aqueous HCl (1M, 50ml), saturated $NaHCO_3$ (50ml) and water (50ml), dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2; CH_2Cl_2/MeOH, 93:7) gave the title compound as a colourless gum (2.79g, 53%). δH (DMSO-d^6) (spectrum complex due to presence of rotamers and diastereoisomers) 9.2 (br m) and 8.9 (br m) together (1H, CONH), 5.75-492 (2H, m, 2 x CH_α), 4.74 (d, J 8.8Hz) and 4.73 (d, J 9.7Hz) and 4.53 (d, J 8.6HZ) and 4.52 (d, J 8.6Hz) and 4.32 (d. J 9.7Hz) and 4.31 (d, J 9.8Hz) together (2H, NCH_2S), 3.74-3.67 (several S, 9H, CO_2Me + $P(OMe)_2$), 3.49 (dd, J 7.3, 11.8Hz) and 3.35-3.26 (m) and 3.14-3.07 (m) and 2.97 (dd, J 4.4, 11.9Hz) together (2H, $CHCH_2S$), 2.061 (s) and 2.057 (s) and 1.92 (s) and 1.91 (s) together (3H, $NCOCH_3$); m/z (ESI, 60V) 355 (M^++1).

INTERMEDIATE 2

3,5-Dichloro-N^4-(4-formylphenyl)isonicotinamide

A mixture of 3,5-dichloroisonicotinic acid (2.88g, 15mmol) and thionyl chloride (30ml) was heated to reflux. A few drops of DMF were added and the suspension refluxed for 2h to give a slightly yellow solution. Excess reagent was removed under reduced pressure and the residue azeotroped with toluene (2 x 50ml) to give 3,5-dichloroisonicotinoyl chloride. This was dissolved in CH_2Cl_2 (50ml) and added to a solution of 4-aminobenzyl alcohol (1.60g, 13mmol) and NMM (1.65ml, 15mmol) in CH_2Cl_2 (50ml). The mixture was stirred at room temperature overnight. Manganese IV oxide (activated, <5micron, ~85%, 22g) was added to the resulting suspension. The mixture was stirred at room temperature for 6h then filtered through Celite®. The filtrate was washed with dilute hydrochloric acid (1M, 50ml) and saturated aqueous sodium hydrogen carbonate (50ml), dried (Na_2SO_4) and evaporated under reduced pressure to give the title compound (2.40g, 63%) as a pale yellow solid. δH (DMSO-d^6) 11.35 (1H, s, CHO), 9.95 (1H, s, CONH), 8.83 (2H, s, pyH), 7.96 (2H, d, J 8.7,Hz, ArH) and 7.88 (2H, d, J 8.7Hz, ArH); m/z (ESI, 60V) 295 (M^++ 1).

INTERMEDIATE 3

***N*-(Trimethylacetyl)-α-phosphonoglycine trimethyl ester**

A mixture of *N*-(benzyloxycarbonyl)-α-phosphonoglycine trimethyl ester (Aldrich, 5g, 15mmol) and palladium on charcoal (10% pd, 1.0g) in methanol 60ml) was stirred under a hydrogen atmosphere (balloon) at room temperature for 2h. The mixture was filtered through Celite® and the filtrate evaporated under reduced pressure to give the corrsponding amine. This amine was dissolved in CH_2Cl_2 (75ml) at 0°. NMM (1.65ml, 15mmol) and trimethylacetyl chloride (1.85ml, 15mmol) were added and the mixture stirred at room temperature overnight. The mixture was diluted with CH_2Cl_2 (300ml), washed with dilute hydrochloric acid (1M, 50ml) and saturated aqueous sodium hydrogen carbonate (50ml), dried (Na_2SO_4) and evaporated under reduced pressure to give the title compound as a white waxy solid (4.0g, 95%). δH (DMSO-d^6) 8.08 (1H, br d, J 8.9Hz, CONH), 5.15 (1H, dd, J 23.7, 9.0Hz, CHα), 3.73-3.67 (9H, m, CO_2Me + $P(OMe)_2$) and 1.14 (9H, s, Me_3CCO); m/z (ESI, 60V) 282 (M^++ 1).

INTERMEDIATE 4

***N*-(2-Chloronicotinoyl)-α-phosphonoglycine trimethyl ester**

A mixture of *N*-(benzyloxycarbonyl)-α–phosphonoglycine trimethyl ester (Aldrich, 4.86g, 14.7mmol) and palladium on charcoal (10% Pd, 2g) in MeOH (60ml) was stirred under a hydrogen atmosphere (balloon) for 4h. The mixture was filtered through Celite® and the filtrate evaporated under reduced pressure to give the corresponding amine. 2-Chloronicotinoyl chloride (14.7mmol, 2.59g) was added to a solution of the amine and NMM (1.65ml, 15mmol) in CH_2Cl_2 (75ml) at 0°. The mixture was stirred overnight at room temperature, diluted with CH_2Cl_2 (300ml), washed with dilute hydrochloric acid (50ml) and saturated $NaHCO_3$ (50ml), dried (Na_2SO_4) and evaporated under reduced pressure to give the title compound as a colourless viscous gum (4.54g, 91%). δH (DMSO-d^6) 9.67 (1H, dd, J 8.9,. 2.8Hz, CONH), 8.49 (1H, dd, J 4.8, 2.0Hz, ArH), 7.82 (1H, dd, J 7.5, 2.0Hz, ArH), 7.50 (1H, dd, J 7.5, 4.8Hz), 5.28 (1H, dd, J 22.9, 8.9Hz, CHα) and 3.82-3.73 (9H, m, CO_2Me + $P(OMe)_2$); m/z (ESI, 60V) 337 (M^++ 1).

INTERMEDIATE 5

2-(2-Chloro-3-pyridinyl)-4-[(Z)-1-(4-nitrophenyl)ethylidene]-1,3-oxazol-5-one

A mixture of 2-{[(2-chloro-3-pyridinyl)carbonyl]amino}acetic acid (6.44g, 30mmol, prepared from glycine and 2-chloronicotinoyl chloride), 4-nitroacetophenone (2.48g, 15mmol), lead (IV) acetate (3.33g, 7.5mmol) and acetic anhydride in THF (30ml) was heated at reflux for 4 days. The mixture was poured onto crushed ice, the solid filtered off, washed with water and dried. The brown solid was triturated twice with boiling ethanol and filtered off to give the title compound as a brown solid (1.07g). δ_H ($CDCl_3$), 8.57 (1H, dd, J 4.8, 2.1Hz, PyH), 8.34-8,29 (3H, m, ArH + PyH), 8.05 (2H, d, J 9.1Hz, ArH), 7.41 (1H, dd, J 7.9, 4.8Hz, PyH) and 2.84 (3H, s, Me).

INTERMEDIATE 6

Ethyl (Z)-3-(4-aminophenyl)-2-{[(2-chloro-3-pyridinyl)carbonyl]amino}-2-butenoate

A mixture of Intermediate 5 (840mg, 2.45mmol) and tin(II) chloride dihydrate (2.76g, 12.2mmol) in ethanol (50ml) was heated at reflux for 2h. The solvent was removed *in vacuo*. CH_2Cl_2 (100ml) was added to the residue and the resulting suspention treated with sodium carbonate (50ml). The mixture was filtered and the filtrate extracted with CH_2Cl_2 (100ml). The organic extract was dried (Na_2SO_4) and evaporated *in vacuo*. Chromatography (SiO_2; CH_2Cl_2/MeOH, 95:5) gave the title compound as a yellow foam (213mg) (also contained some of the *E* isomer, Z:*E* 85:15 determined by HNMR). δ_H ($CDCl_3$), 8.41 (1H, dd, J 4.7, 2.0Hz,PyH), 8.03 (1H, dd, J 7.7, 2.0Hz, PyH), 7.65 (1H, br s, CONH), 7.29 (1H, dd, J 7.7, 4.8Hz, PyH), 7.11 (2H, d, J 8.6Hz, PyH), 6.65 (2H, d,J 8.6Hz, ArH), 4.34 (2H, q, J 7.1Hz, $CO_2C\underline{H}_2CH_3$), 3.77 (2H, v br s, NH_2),2.32 (3H, s, Me) and 1.35 (3H, t, J 7.1Hz, $CO_2CH_2C\underline{H}_3$); m/z (ESI, 60V) 360 (MH^+).

INTERMEDIATE 7

4-[(3,5-Dichloro-4-pyridinyl)methoxy]benzaldehyde

A mixture of 4-(bromomethyl)-3,5-dichloropyridine (15g, 62.2mmol), 4-hydroxybenzaldehyde (7.97g, 65.4mmol) and caesium carbonate (22.3g, 68.5mmol) in DMF (150ml) was stirred for 4.5h at room temperature. The mixture was poured into water and extracted with EtOAc. The organic extract was washed with sodium carbonate solution (x2) and brine, dried ($MgSO_4$) and evaporated *in vacuo* to give the title compound as a brown solid (16g). δ_H (DMSO-d^6), 9.91 (1H, s), 8.74 (2H, s), 7.91 (2H, d, J 8.6Hz), 7.27 (2H, d, J 8.6Hz), 5.37 (2H, s); m/z (ESI) 282 (MH^+).

INTERMEDIATE 8

Methyl 2-(diethoxyphosphino)-2-[(2,6-dimethoxybenzoyl) amino]acetate

2,6-Dimethoxybenzoyl chloride (1.28g, 6.42mmol) was added to a mixture of methyl 2-amino-2-(diethoxyphosphino)acetate hydrochloride [1.5g, 6.11mmol, prepared by the method of Y. Nasukawa, *et al*, J. Org. Chem, (1992) 57, 5453] and NMM (1.5ml, 13.44mmol) in CH_2Cl_2 (30ml). The mixture was stirred overnight at room temperatue then poured into 10% citric acid. The mixture was extracted with CH_2Cl_2 (x2) and the combined organic extracts washed with sodium hydrogen carbonate solution (x2) and brine, dried ($MgSO_4$) and evaporated *in vacuo* to give a brown solid

(1.62g). δ_H (DMSO-d^6) 8.82 (1H, dd, J 9.1, 2.5Hz), 7.29 (1H, t, J 8.4Hz), 6.65 (2H, d, J 8.4Hz), 5.20 (1H, dd, J 20.0, 9.2Hz), 4.15-4.03 (4H, m), 3.72 (3H, s), 3.71 (6H, s), 1.39-1.20 (6H, m); m/z (ESI) 390 (MH^+).

EXAMPLE 1

***N*-Acetyl-*D*-thioproline-4-[(3,5-dichloroisonicotinoyl)amino]-*Z*-didehydrophenylalanine methyl ester**

DBU (173µl, 1.15mmol) was added to a solution of Intermediate 1 (407mg, 1.15mmol) and Intermediate 2 (339mg, 1.15mmol) in CH_2Cl_2 (12ml). The mixture was stirred at room temperature overnight then diluted with CH_2Cl_2 (100ml), washed with dilute hydrochloric acid (1M, 30ml), dried (Na_2SO_4) and evaporated under reduced pressure. Column chromatrography (SiO_2; EtOAc/MeOH, 98:2) gave the title compound as a white foam (555mg, 92%) contaminated with a few percent of its double bond isomer (by NMR). Crystallization from EtOAc gave the pure title compound as poorly formed white crystals (400mg) m.p. 155-158°. δH (DMSO-d^6, 390K) 9.2 (1H, b r s, CHCONH), 8.71 (2H, s, PyH), 7.67 (4H, s, ArH), 7.34 (1H, s C=CH), 4.99 (1H, dd, J 7.3, 4.0Hz, CHαthiopro), 4.81 (1H, d, J 9.1Hz, NCH_AH_BS), 4.54 (1H, d, J 9.1Hz, NCH_AH_BS), 3.75 (3H, s, CO_2Me), 3.41 (1H, dd, J 11.6, 7.3Hz, $CHCH_AH_BS$), 3.26 (1H, dd, J 11.6, 3.9Hz, $CHCH_AH_BS$) and 2.11 (3H, s, $COCH_3$) (pyCONH not observed); m/z (ESI, 60V) 523 (M^++ 1).

EXAMPLE 2

***N*-Acetyl-*D*-thioproline-4-[(3,5-dichloroisonicotinoyl)amino]-*Z*-didehydrophenylalanine**

Lithium hydroxide monohydrate (35mg, 0.844mmol) was added to a solution of the compound of Example 1 (368mg, 0.704mmol) in a mixture of dioxane (10ml) and water (10ml). The mixture was stirred at room temperature for 48h. Dioxane was removed under reduced pressure and the aqueous residue acidified with glacial acetic acid. The precipitate produced was filtered off then freeze-dried from a mixture of methanol and water to give the title compound as a white fluffy solid (220mg, 61%). δH (DMSO-d^6, 390K) 10.6 (1H, br s, pyCONH), 8.70 (2H, s, PyH), 7.64 (4H, s, ArH), 7.34 (1H, s, C=CH), 4.99 (1H, dd, J 7.3, 4.0Hz, CHαthiopro), 4.81 (1H, d, J 9.1Hz, NCH_AH_BS), 4.53 (1H, d, J 9.1Hz, NCH_AH_BS), 3.40 (1H,

dd, J 11.6, 7.4Hz, $CHCH_AH_BS$), 3.27 (1H, dd, J 11.6, 4.0Hz, $CHCH_AH_BS$) and 2.11 (3H, s, $COCH_3$) (acid proton and CHCONH not observed); m/z (ESI, 60V) 509 (M^++ 1).

EXAMPLE 3

***N*-Acetyl-*D*-thioproline-4-[(3,5-dichloroisonicotinoyl)amino]-*E*-didehydrophenylalanine methyl ester**

A solution of Intermediate 1 (708mg, 2mmol) in THF (10ml) was added to a solution of LDA (2M solution, Aldrich, 1ml, 2mmol) in THF (5ml) at -78°. The suspension was warmed to 0° and a solution of Intermediate 2 (590mg, 2mmol) in THF (5ml) was added followed by DMF (2ml) to dissolve the precipitate. The mixture was stirred at room temperature ovenight. The solvents were removed under reduced pressure. The residue was dissolved in EtOAc (200ml), washed with water (2 x 50ml) and brine (50ml), dried (Na_2SO_4) and evaporated under reduced pressure. The crude product contained a mixture of double bond geometric isomers: E/Z, ~35/65 determined by NMR. Column chromatography (SiO_2; EtOAc/MeOH, 97:3) gave some of the less polar E isomer - the title compound (125mg) as a white solid. δH (DMSO-d^6, 390K) 10.56 (1H, s, pyCONH), 9.55 (1H, s, CHCONH), 8.71 (2H, s, pyH), 7.61 (2H, br d, J 7.9Hz, ArH), 7.30 (2H, d, J 8.5Hz, ArH), 6.86 (1H, s, C=CH), 4.94 (1H, dd, J 7.3, 3.9Hz, CHαthiopro), 4.80 (1H, d, J 9.1Hz, NCH_AH_BS), 4.53 (1H, d, J 9.1Hz, NCH_AH_BS), 3.67 (3H, s, CO_2Me), 3.39 (1H, dd, J 11.6, 7.3Hz, $CHCH_AH_BS$), 3.32 (1H, dd, J 11.6, 3.9Hz, $CHCH_AH_BS$) and 2.10 (3H, s, $COCH_3$); m/z (ESI, 60V) 523 (M^++ 1).

EXAMPLE 4

***N*-Acetyl-*D*-thioproline-4-[(3,5-dichloroisonicotinoyl)amino]-*E*-didehydrophenylalanine**

Lithium hydroxide monohydrate (11mg, 0.25mmol) was added to a solution of the compound of Example 3 (110mg, 0.21mmol) in a mixture of dioxane (5ml) and water (5ml). The mixture was stirred at room temperature for 24h. The dioxane was removed under reduced presure. The aqueous residue was acidified with glacial acetic acid. The precipitate formed was filtered off and freeze-dried from a mixture of methanol and water to give the title compound as a pale yellow solid (56mg, 52%). δH (DMSO-d^6,

390K) 10.53 (1H, s, pyCONH), 9.33 (1H, s, CHCONH), 8.70 (2H, s, pyH), 7.58 (2H, br d, J 7.7Hz, ArH), 7.37 (2H, d, J 8.5Hz, ArH), 6.99 (1H, s, C=CH), 4.96 (1H, dd, J 7.3, 3.9Hz, CHαthiopro), 4.81 (1H, d, J 9.1Hz, NCH_AH_BS), 4.53 (1H, d, J 9.1Hz, NCH_AH_BS), 3.39 (1H, dd, J 11.6, 7.3Hz, $CHCH_AH_BS$), 3.24 (1H, dd, J 11.6, 3.9Hz, $CHCH_AH_BS$) and 2.10 (3H, s, $COCH_3$) (acid proton not observed); m/z (ESI, 60V) 509 (M^++ 1).

The geometry of the double bond was confirmed as *E* by observation of an n.O.e. between the olefinic proton and the NH of the central amide bond. No n.O.e was seen between the corresponding protons in the *Z* double bond compound.

EXAMPLE 5

***N*-Trimethylacetyl-4-[(3,5-dichloroisonicotinoyl)amino]-*Z*-didehydrophenylalanine methyl ester**

DBU (22μl, 1.5mmol) was added to a solution of Intermediate 3 (422mg, 1.5mmol) and Intermediate 2 (443mg, 1.5mmol) in CH_2Cl_2 (15ml). The mixture was stirred at room temperature overnight, diluted with CH_2Cl_2 (20ml), washed with dilute hydrochloric acid (1M, 30ml), dried (Na_2SO_4) and evaporated under reduced pressure. The solid obtained was re-suspended in CH_2Cl_2 (~10ml) and filtered off to give the title compound as a white solid (356mg, 53%). δH (DMSO-d^6) 11.09 (1H, s, ArCONH), 9.09 (1H, s, *t*-BuCONH), 8.81 (2H, s, pyH), 7.67 (4H, s, ArH), 7.26 (1H, s, C=CH), 3.70 (3H, s, CO_2Me) and 1.21 (9H,s, *t*-Bu); m/z (ESI, 60V) 450 (M^++ 1).

EXAMPLE 6

***N*-Trimethylacetyl-4-[(3,5-dichloroisonicotinoyl)amino]-*Z*-didehydrophanylalanine**

Lithium hydroxide monohydrate (65mg, 1.56mmol) was added to the compound of Example 5 (350mg, 0.778mmol) in a mixture of dioxane (8ml) and water (8ml). The solution was stirred at room temperature overnight. The dioxane was removed under reduced pressure and the acqueous residue acidified (1M hydrochloric acid, pH1). The precipitate formed was filtered off, washed with water and dried to give the title compound as a white solid (300mg, 88%). δH (DMSO-d^6) 12.49 (1H, br s, CO_2H), 11.07 (1H, s, ArCONH), 8.93 (1H, s, *t*-BuCONH), 8.81 (2H, s,

pyH), 7.67 (2H, d, J 9.1Hz, ArH), 7.63 (2H, d, J 9.1Hz, ArH), 7.28 (1H, s, C=CH) and 1.20 (9H, s, *t*-Bu); m/z (ESI, 60V) 436 (M^++ 1).

EXAMPLE 7

***N*-Trimethylacetyl-4-[(3,5-dichloroisonicotinoyl)amino]-*E*-didehydrophenylalanine methyl ester**

A solution of Intermediate 3 (562mg, 2mmol) in THF (10ml) was added to a solution of LDA (2M solution, Aldrich, 1.0ml, 2mmol) in THF (5ml) at -78°. The solution was warmed slowly to 0° and a solution of Intermediate 2 (590mg, 2mmol) in THF (5ml) was added. The mixture was stirred at room temperature overnight. Water (50ml) was added and the mixture extracted with CH_2Cl (2 x 150ml). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The crude product contained a mixture of double bond geometric isomers, E/Z ~40/60 determined by NMR. Column chromatography (SiO_2; CH_2Cl_2/MeOH, 95:5) followed by chromatotron separation (SiO_2; EtOAc/hexane, 50/50) gave some of the less polar, *E* isomer, the title compound (130mg). δH (DMSO-d^6) 10.98 (1H, s, ArCONH), 9.52 (1H, s, *t*-BuCONH), 8.80 (2H, s, pyH), 7.62 (2H, d, J 8.6Hz, ArH), 7.22 (2H, d, J 8.6Hz, ArH), 6.56 (1H, s, C=CH), 3.62 (3H, s, CO_2Me) and 1.16 (9H, s, *t*-Bu); m/z (ESI, 60V) 450 (M^++ 1).

EXAMPLE 8

***N*-Trimethylacetyl-4-[(3,5-dichloroisonicotinoyl)amino]-*E*-didehydrophenylalanine**

Lithium hydroxide monohydrate (22mg, 0.533mmol) was added to the compound of Example 7 (120mg, 0.26mmol) in a mixture of dioxane (5ml) and water (5ml). The solution was stirred at room temperature overnight. The dioxane was removed under reduced pressure and the aqueous residue acidified (1M hydrochloric acid). The precipitate formed was filtered off, washed with water and dried to give the title compound as a white solid (87mg). δH (DMSO-d^6) 12.67 (1H, br s, CO_2H), 10.96 (1H, s, ArCONH), 9.33 (1H, s, *t*-BuCONH), 8.80 (2H, s, pyH), 7.59 (2H, d, J 8.7Hz, ArH), 7.32 (2H, d, J 8.7Hz, ArH), 6.55 (1H, s, C=CH) and 1.17 (9H, s, *t*-Bu); m/z (ESI, 60V) 436 (M^++ 1).

EXAMPLE 9

***N*-(2-Chloronicotinoyl)-4-[(3,5-dichloroisonicotinoyl)amino]-Z-didehydrophenylalanine methyl ester**

DBU (22µl, 1.5mmol) was added to a solution of Intermediate 4 (508mg, 1.5mmol) and Intermediate 2 (443mg, 1.5mmol) in CH_2Cl_2 (15ml). The mixture was stirred at room temperature overnight, diluted with CH_2Cl_2 (200ml), washed with dilute hydrochloric acid (50ml), dried (Na_2SO_4) and evaporated under reduced pressure. Column chromatography (SiO_2, CH_2Cl_2/MeOH; 95:5 to 90:10) gave the product as a yellow viscous oil. Crystallisation from MeOH gave the title compound (418mg) as small off-white crystals m.p. 223-224°. δH (DMSO-d^6) 11.13 (1H, br s, ArCONHAr), 10.32 (1H, br s, pyCONHC=C), 8.81 (2H, s, pyH), 8.54 (1H, dd, J 4.8, 1.8Hz, pyH), 8.01 (1H, dd, J 7.5, 1.9Hz, pyH), 7.79 (2H, d, J 8.8Hz, ArH), 7.72 (2H, d, J 8.8Hz, ArH), 7.59 (1H, dd, J 7.5, 4.8Hz, pyH), 7.43 (1H, s, C=CH) and 3.79 (3H, s, CO_2Me); m/z (ESI, 60V) 505 (M^++ 1).

EXAMPLE 10

a) ***N*-(2-Chloronicotinoyl)-4-[(3,5-dichloroisonicotinoyl)amino]-Z-didehydrophenylalanine**

Lithium hydroxide monohydrate (68mg, 1.61mmol) was added to the compound of Example 9 (407mg, 0.805mmol) in a mixture of dioxane (8ml) and water (8ml). The reaction mixture was stirred at room temperature for 24h. The dioxane was evaporated under reduced pressure. The aqueous residue was acidified (dilute hydrochloric acid) and the precipitate formed filtered off, washed with water and dried to giver the title compound as an off-white solid (354mg, 89%). δH (DMSO-d^6) 11.14 (1H, br s, CO_2H), 11.11 (1H, s, pyCONHAr), 10.16 (1H, s, pyCONHC=C), 8.81 (2H, s, pyH), 8.53 (1H, dd, J 4.8, 1.8Hz, pyH), 7.97 (1H, dd, J 7.5, 1.8Hz, pyH), 7.77 (2H, d, J 8.8Hz, ArH), 7.71 (2H, d, J 8.8Hz, ArH), 7.58 (1H, dd, J 7.5, 4.8Hz, pyH) and 7.44 (1H, s, C=CH); m/z (ESI, 60V) 491 (M^++ 1).

The following compounds of Examples 10b) and 10c) were prepared in a similar manner by hydrolysis of the corresponding methyl ester:

b) (Z)-3-{4-[(3,5-Dichloro-4-pyridinyl)methoxy]phenyl}-2-[(2,6-dimethoxybenzoyl)amino]-2-propenoic acid

prepared as an off-white solid: δ_H (DMSO-d^6), 12.4 (1H, br s), 9.53 (1H,s), 8.73 (2H, s), 7.83 (2H, d, J 8.8Hz), 7.32 (1H, t, J 8.3Hz), 7.25 (1H, s), 7.09 (2H, d, J 8.8Hz), 6.70 (2H, d, J 8.4Hz), 5.31 (2H, s), 3.79 (6H, s); m/z (ESI) 503 (MH^+). The ester starting material was prepared from Intermediate 7 and Intermediate 8 in a similar manner to the compounds of Example 9.

c) (Z)-2-[[(2-Chloro-3-pyridinyl)carbonyl]amino}-3-{4-[(3,5-dichloro-4-pyridinyl)methoxy]phenyl}-2-propenoic acid

prepared as a pale yellow solid. δ_H (DMSO-d^6), 12.8 (1H, br s), 10.09 (1H, s), 8.73 (2H, s), 8.52 (1H, dd, J 4.9, 1.9Hz), 7.93 (1H, dd, J 7.6, 1.9Hz), 7.75 (2H, d, J 8.9Hz), 7.56 (1H,dd, J 7.6, 4.9Hz), 7.46 (1H,s), 7.13 (2H, d, J 8.9Hz), 5.29 (2H, s); m/z (ESI) 480 (MH^+). The ester starting material was prepared from Intermediate 4 and Intermediate 7 in a similar manner to the compound of Example 9.

EXAMPLE 11

N-(2-Chloronicotinoyl)-4-[(3,5-chloronicotinoyl)amino]-*E*-didehydrophenylalanine methyl ester

A solution of Intermediate 4 (1.83g, 5mmol) in THF (15ml) was added to a solution of LDA (2M, Aldrich, 2.5ml, 5mmol) in THF (15ml) at -78°. The solution was warmed slowly to 0° and a solution of Int ermediate 2(1.48g, 5mmol) in THF (15ml) was added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure and the residue dissolved in EtOAc (300ml), washed with dilute hydrochloric acid (50ml), water (50ml) and brine (50ml), dried (Na_2SO_4) and evaporated under reduced pressure. Column chromatography (SiO_2; CH_2Cl_2/MeOH, 93:7) gave the title compound as a mixture with the corresponding Z isomer (1.80g). (E:Z ~ 40/60 by NMR). Further purification of a small portion by chromatotron (SiO_2; CH_2Cl_2/MeOH, 98:2) gave a small sample of the pure title compound free from its *Z* isomer. δH (DMSO-d^6) 11.03 (1H, s, pyCONHAr), 10.74 (1H, s, pyCONHC=C), 8.80 (2H, s, pyH), 8.55 (1H, dd, J4.8, 1.9Hz, pyH), 8.02 (1H, dd, J 7.5, 1.9Hz, pyH), 7.65 (2H, d, J 8.6Hz, ArH), 7.56 (1H, dd, J 7.5, 4.8Hz, pyH), 7.30

(2H, d, J 8.7Hz, ArH), 6.70 (1H, s, C=CH) and 4.71 (3H, s, CO_2Me); m/z (ESI, 60V) 505 (M^++ 1).

EXAMPLE 12

***N*-(2-Chloronicotinoyl)-4-[(3,5-dichloroisonicotinoyl)amino]-*E*-didehydrophenylalanine**

Lithium hydroxide monohydrate (161mg, 3.83mmol) was added to a solution of the compound of Example 11 [mixture of E + Z isomers E:Z ~ 40:60] (967mg, 1.91mmol) in dioxane (15ml) and water (15ml). The mixture was stirred at room temperature overnight then refluxed for 30min. The dioxane was evaporated under reduced pressure. The aqueous residue was acidified (dilute hydrochloric acid) and the precipitate formed filtered off, washed with water and dried to give the title compound as a mixture with the corresponding *Z* isomer. Purification by preparative HPLC (Waters C18 symmetry column; 1.00ml/min; MeCN/H_2O 0.1% trifluoroacetic acid) gave a pure sample of the *E* isomer title compound as a pale yellow powder. δH (DMSO-d^6) 13.09 (1H, v br s, CO_2H), 11.00 (1H, s, ArCONHAr), 10.54 (1H, s, pyCONHC=C), 8.80 (2H, s, pyH), 8.53 (1H, dd, J, 4.8, 1.9Hz, pyH), 8.00 (1H, dd, J 7.5, 1.9Hz, pyH), 7.63 (2H, d, J 8.6Hz, ArH), 7.56 (1H, dd, J 7.5, 4.8Hz, ArH), 7.37 (2H, d, J 8.7Hz, ArH) and 6.73 (1H, s, C=CH); m/z (ESI, 60V) 491 (M^++ 1).

EXAMPLE 13

Methyl 3-bromo-2-{[(2-chloro-3-pyridinyl)carbonyl]amino}-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-propenoate

A suspension of the compound of Example 9 (1.258g, 2.49mmol) and *N*-bromosuccinimide (487mg, 2.74mmol) in CH_2Cl_2 (25ml) was stirred in the dark overnight at room temperature. Triethylamine (693µl, 4.98mmol) was added and the solution stirred for a further 4h. The mixture was diluted with CH_2Cl_2 (300ml) and washed with dilute HCl, sodium carbonate solution and sodium thiosulphate solution, dried (Na_2SO_4) and concentrated *in vacuo*. The NMR spectrum of the crude reaction mixture showed the presence of both *E* and *Z* isomers (ratio ~60:40). Chromatography (SiO_2; CH_2Cl_2/MeOH, 93:7) followed by crystallisation from EtOAc gave the less polar isomer (Isomer A) of the title compound (298mg). The crude liquors were concentrated *in vacuo* and crystallisation

from EtOAc/hexane gave the more polar isomer (Isomer B) of the title compound (204mg).

ISOMER A

δ_H (DMSO-d^6), 11.12 (1H, br s, CONH), 10.65 (1H, br s, CONH), 8.81 (2H, s,Cl_2PyH), 8.55 (1H,dd, J 4.8, 1.9Hz, PyH), 7.96 (1H,dd, J 7.6, 1.9Hz, PyH), 7.71 (2H, d, J 8.7Hz, ArH), 7.57 (1H, dd, J 7.5, 4.8Hz, PyH), 7.39 (2H, d, J 8.6Hz, ArH) and 3.55 (3H, s, CO_2Me); m/z (ESI) 585 (MH^+).

ISOMER B

δ_H (DMSO-d^6), 11.14 (1H, br s, CONH), 10.45 (1H, v br s, CONH), 8.80 (2H, s, Cl_2PyH), 8.48 (1H, dd, J 4.8,1.9Hz, PyH), 7.82 (1H, dd, J 7.6, 1.9Hz, PyH), 7.73 (2, d, J 8.4Hz, ArH), 7.53 (2H, d, J 8.4Hz, ArH), 7.50 (1H, dd, J 7.6, 4.9Hz, PyH) and 3.80 (3H, s,CO_2Me); m/z (ESI) 585 (MH^+).

EXAMPLE 14

Methyl 2-{[(2-chloro-3-pyridinyl)carbonyl]amino}-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-3-phenylacrylate

Tetrakis(triphenylphosphine)palladium (O) (10mol%, 58mg) was added to a mixture of the compound of Example 13, Isomer A (288mg, 0.493mmol) and phenyl boronic acid (90mg, 0.74mmol) in DME (10ml) and sodium carbonate (2M, 0.986mmol, 0.493ml). The mixture was heated at 80° overnight, dlute with CH_2Cl_2 (200ml), washed with diluted HCl and sodium hydrogen carbonate solution, dried (Na_2SO_4) and evaporated *in vacuo*. Chromatography (SiO_2; CH_2Cl_2/MeOH, 93:7) gave the title compound as a white solid (133mg). δ_H (DMSO-d^6), 11.04 (1H, s, CONH), 10.40 (1H, s, CONH), 8.79 (2H, s, Cl_2PyH), 8.48 (1H, dd, J 4.9, 1.9Hz, PyH), 7.85 (1H, dd, J 7.5, 1.9Hz, PyH), 7.66 (2H, d, J 8.7Hz, ArH), 7.51 (1H, dd, J 7.5,4.9Hz, PyH), 7.39-7.35 (3H, m, ArH), 7.23 (2H, d, J 8.7Hz, ArH), 7.07 (2H, m, ArH) and 3.45 (3H, s, CO_2Me); m/z (ESI, 60V) 581 (MH^+).

EXAMPLE 15

2-{[(2-Chloro-3-pyridinyl)carbonyl]amino}-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-3-phenylacrylic acid

Lithium hydroxide monohydrate (18mg, 0.43mmol) was added to the compound of Example 14 (125mg, 0.215mmol) in a mixture of dioxane (5ml) and water (5ml). The mixture was heated at reflux for 2h. The dioxane was removed *in vacuo* and the aqueous residue acidified with

dilute HCl, the precipitate formed was filtered off, washed with water and dried to give the title compound as a pale yellow solid (96mg). δ_H (DMSO-d^6), 12.53 (1H, br s, CO_2H), 11.02 (1H, s, ArCONHAr), 10.24 (1H, s, ArCONHC=C), 8.79 (2H, s PyH), 8.48 (1H, dd, J 4.8, 1.9Hz, PyH), 7.82 (1H, dd, J 7.5, 1.9Hz, PyH), 7.65 (2H, d, J 8.7Hz, ArH), 7.51 (1H, dd, J 7.5, 4.8Hz, PyH), 7.35-7.34 (3H, m, Ph), 7.21 (2H, d, J 8.6Hz, ArH) and 7.14-7.11 (2H, m, Ph); m/z (ESI, 60V) 567 (MH^+)

EXAMPLE 16

Ethyl (Z)-2-{[(2-chloro-3-pyridinyl)carbonyl]amino}-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-butenoate

A solution of 3,5-dichloroisonicotinoyl chloride (123mg, 0.584mmol) in CH_2Cl_2 (2ml) was added to Intermediate 6 (210mg, 0.584mmol) and NMM (67µl, 0.613mmol) in CH_2Cl_2 (10ml) at 0°. The mixture was stirred for 24h at room temperature, diluted with CH_2Cl_2 (100ml), washed with dilute HCl and sodium hydrogen carbonate solution, dried (Na_2SO_4) and evaporated *in vacuo*. Chromatography (SiO_2; CH_2Cl_2/MeOH, 93:7) gave the title compound as a yellow glass (286mg) (contains some *E* isomer. *Z*:*E*~85:15). δ_H (DMSO-d^6), 11.01 (1H, s, CONH), 9.89 (1H, s, CONH), 8.80 (2H, s, PyH), 8.45 (1H, dd, J 4.8, 1.9Hz, yH), 7.71-7.66 (3H, m, ArH + PyH), 7.48 (1H, dd, J 87, 4.8Hz, PyH), 7.40 (2H, d, J 8.6Hz, PyH), 4.21 (2H,q, J 7.1Hz, $CO_2CH_2CH_3$), 2.31 (3H, s,Me) and 1.26 (3H, t, J 7.1Hz, $CO_2CH_2CH_3$).

EXAMPLE 17

(Z)-2-{[(2-Chloro-3-pyridinyl)carbonyl]amino}-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-butenoic acid

Lithium hydroxide monohydrate (4.4mg, 1.05mml) was added to Ithe compound of Example 16 (280mg, 0.525mmol) in a mixture of dioxane (10ml) and water (10ml). The mixture was heated at reflux for 2h. The dioxane was removed *in vacuo*, the aqueous residue acidified with dilute HCl, the precipitate formed filtered off, washed with water and dried to give a brown solid. Trituration with hot methanol gave the title compound as a pale brown solid (94mg). δ_H (DMSO-d^6), 12.75 (1H,v br s,CO_2H), 10.99 (1H,s, CONH), 9.75 (1H,s, CONH), 8.79 (2H, s, PyH), 8.44 (1H, dd, J 4.8, 1.9Hz, PyH), 7.68-7.64 (3H, m, ArH + PyH), 7.46 (1H, dd, J 7.5,

4.8Hz,PyH), 7.38 (2H, d, J 8.6Hz, ArH) and 2.33 (3H, s, Me); m/z (ESI, 70V) 505 (MH^+).

The following assays can be used to demonstrate the potency and selectivity of the compounds according to the invention. In each of these assays an IC_{50} value was determined for each test compound and represents the concentration of compound necessary to achieve 50% inhibition of cell adhesion where 100% = adhesion assessed in the absence of the test compound and 0% = absorbance in wells that did not receive cells.

$\alpha_4\beta_1$ Integrin-dependent Jurkat cell adhesion to VCAM-Ig

96 well NUNC plates were coated with $F(ab)_2$ fragment goat anti-human IgG Fcγ-specific antibody [Jackson Immuno Research 109-006-098: 100 µl at 2 µg/ml in 0.1M $NaHCO_3$, pH 8.4], overnight at 4°. The plates were washed (3x) in phosphate-buffered saline (PBS) and then blocked for 1h in PBS/1% BSA at room temperature on a rocking platform. After washing (3x in PBS) 9 ng/ml of purified 2d VCAM-Ig diluted in PBS/1% BSA was added and the plates left for 60 minutes at room temperature on a rocking platform. The plates were washed (3x in PBS) and the assay then performed at 37° for 30 min in a total volume of 200 µl containing 2.5×10^5 Jurkat cells in the presence or absence of titrated test compounds.

Each plate was washed (2x) with medium and the adherent cells were fixed with 100µl methanol for 10 minutes followed by another wash. 100µl 0.25% Rose Bengal (Sigma R4507) in PBS was added for 5 minutes at room temperature and the plates washed (3x) in PBS. 100µl 50% (v/v) ethanol in PBS was added and the plates left for 60min after which the absorbance (570nm) was measured.

$\alpha_4\beta_7$ Integrin-dependent JY cell adhesion to MAdCAM-Ig

This assay was performed in the same manner as the $\alpha_4\beta_1$ assay except that MAdCAM-Ig (150ng/ml) was used in place of 2d VCAM-Ig and a sub-line of the β-lympho blastoid cell-line JY was used in place of Jurkat cells. The IC_{50} value for each test compound was determined as described in the $\alpha_4\beta_1$ integrin assay.

$\alpha_5\beta_1$ Integrin-dependent K562 cell adhesion to fibronectin

96 well tissue culture plates were coated with human plasma fibronectin (Sigma F0895) at 5μg/ml in phosphate-buffered saline (PBS) for 2 hr at 37°C. The plates were washed (3x in PBS) and then blocked for 1h in 100μl PBS/1% BSA at room temperature on a rocking platform. The blocked plates were washed (3x in PBS) and the assay then performed at 37°C in a total volume of 200μl containing 2.5x 10^5 K562 cells, phorbol-12-myristate-13-acetate at 10ng/ml, and in the presence or absence of titrated test compounds. Incubation time was 30 minutes. Each plate was fixed and stained as described in the $\alpha_4\beta_1$ assay above.

$\alpha_m\beta_2$-dependent human polymorphonuclear neutrophils adhesion to plastic

96 well tissue culture plates were coated with RPMI 1640/10% FCS for 2h at 37°C. 2 x 10^5 freshly isolated human venous polymorphonuclear neutrophils (PMN) were added to the wells in a total volume of 200μl in the presence of 10ng/ml phorbol-12-myristate-13-acetate, and in the presence or absence of test compounds, and incubated for 20min at 37°C followed by 30min at room temperature. The plates were washed in medium and 100μl 0.1% (w/v) HMB (hexadecyl trimethyl ammonium bromide, Sigma H5882) in 0.05M potassium phosphate buffer, pH 6.0 added to each well. The plates were then left on a rocker at room temperature for 60 min. Endogenous peroxidase activity was then assessed using tetramethyl benzidine (TMB) as follows: PMN lysate samples mixed with 0.22% H_2O_2 (Sigma) and 50μg/ml TMB (Boehringer Mannheim) in 0.1M sodium acetate/citrate buffer, pH 6.0 and absorbance measured at 630nm.

αIIb/β_3 -dependent human platelet aggregation

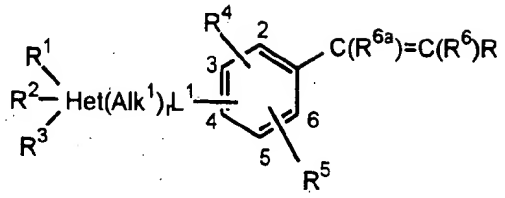
Human platelet aggregation was assessed using impedance aggregation on the Chronolog Whole Blood Lumiaggregometer. Human platelet-rich plasma (PRP) was obtained by spinning fresh human venous blood anticoagulated with 0.38% (v/v) tri-sodium citrate at 220xg for 10 min and diluted to a cell density of 6 x 10^8/ml in autologous plasma. Cuvettes contained equal volumes of PRP and filtered Tyrode's buffer (g/liter: NaCl 8.0; $MgCl_2.H_2O$ 0.427; $CaCl_2$ 0.2; KCl 0.2; D-glucose 1.0; $NaHCO_3$ 1.0;

$NaHPO_4.2H_2O$ 0.065). Aggregation was monitored following addition of 2.5μM ADP (Sigma) in the presence or absence of inhibitors.

In the above assays the preferred compounds of the invention generally have IC_{50} values in the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ assays of 1 μM and below. In the other assays featuring α integrins of other subgroups the same compounds had IC_{50} values of 50μM and above thus demonstrating the potency and selectivity of their action against α_4 integrins.

CLAIMS

1. A compound of formula (1)



(1)

wherein

Het is a heteroaromatic group;

R^1, R^2 and R^3 which may be the same or different is each an atom or group $-L^2(Alk^2)_tL^3(R^7)_u$ in which L^2 and L^3 which may be the same or different is each a covalent bond or a linker atom or group, t is zero or the integer 1, u is an integer 1, 2 or 3, Alk^2 is an aliphatic or heteroaliphatic chain and R^7 is a hydrogen or halogen atom or a group selected from alkyl, $-OR^8$ [where R^8 is a hydrogen atom or an optionally substituted alkyl group], $-SR^8$, $-NR^8R^9$ [where R^9 is as just defined for R^8 and may be the same or different], $-NO_2$, -CN, $-CO_2R^8$, $-OCO_2R^8$, $-CONR^8R^9$, $-OCONR^8R^9$, $-CSNR^8R^9$, $-COR^8$, $-OCOR^8$, $-N(R^8)COR^9$, $-N(R^8)CSR^9$, $-SO_2N(R^8)(R^9)$, $-N(R^8)SO_2R^9$, $-N(R^8)CON(R^9)(R^{10})$, [where R^{10} is a hydrogen atom or an optionally substituted alkyl group] $-N(R^8)CSN(R^9)(R^{10})$ or $-N(R^8)SO_2N(R^9)(R^{10})$;

Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain;

L^1 is a covalent bond or a linker atom or group;

R^4 and R^5, which may be the same or different, is each a hydrogen or halogen atom or an alkyl, alkoxy, hydroxy or nitro group;

R^6 and R^{6a}, which may be the same or different, is each an atom or group $-L^2(Alk^2)_tL^3R^{11}$ in which L^2, L^3, Alk^2 and t are as previously defined and R^{11} is a hydrogen or halogen atom or an $-OR^8$, $-NR^8R^9$, $-NO_2$, -CN, $-CO_2R^8$, $-CONR^8R^9$, $-COR^8$, $-N(R^8)COR^9$, $-N(R^8)CSR^9$, $-SO_2N(R^8)(R^9)$, $-N(R^8)SO_2R^8$, $-N(R^8)CON(R^9)(R^{10})$,

$-N(R^8)CSN(R^9)(R^{10})$, $-N(R^8)SO_2N(R^9)(R^{10})$, or an optionally substituted aliphatic, heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group;
r is zero or the integer 1;
R is a carboxylic acid ($-CO_2H$) or a derivative thereof;
and the salts, solvates, hydrates and N-oxides thereof.

2. A compound according to Claim 1 wherein R^6 and R^{6a} are in a trans relationship to each other.

3. A compound according to Claim 1 or Claim 2 wherein R is a $-CO_2H$ group.

4. A compound according to any one of Claim 1 to Claim 3 wherein R^{6a} is a hydrogen atom.

5. A compound according to any one of Claim 1 to Claim 4 wherein Het is a five- or six-membered monocyclic heteroaromatic group containing one or two heteroatoms selected from oxygen, sulphur or nitrogen atoms.

6. A compound according to Claim 5 wherein Het is a pyridyl or pyrimidinyl group.

7. A compound according to any one of Claim 1 to Claim 6 wherein each of R^1, R^2 and R^3 is a hydrogen atom or an optionally substituted alkyl, $-OR^8$, $-SR^8$, $-NR^8R^9$, $-COR^8$, $-CO_2R^8$, $-NO_2$, or -CN group.

8. A compound according to any one of Claim 1 to Claim 7 wherein $-(Alk^1)_rL^1-$ is a $-CH_2O-$ or $-CON(R^{12})-$ group.

9. A compound according to any of the preceding claims wherein R^6 is a L^2R^{11} or $-L^2Alk^2R^{11}$ atom or group.

10. A compound according to Claim 9 wherein L^2 is a -NHCO-, -NHCS- or -$NHSO_2$- group, Alk^2 is a C_{1-4}alkylene chain and R^{11} is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group.

11. A compound according to Claim 10 wherein R^{11} is an optionally substituted C_{5-7}cycloaliphatic, C_{5-7}heterocycloaliphatic, phenyl or C_{5-7}heteroaromatic group.

12. A compound which is:
N-Acetyl-*D*-thioproline-4-[(3,5-dichloroisonicotinoyl)amino]-*Z*-didehydrophenylalanine;
N-Acetyl-*D*-thioproline-4-[(3,5-dichloroisonicotinoyl)amino]-*E*-didehydrophenylalanine;
N-Trimethylacetyl-4-[(3,5-dichloroisonicotinoyl)amino]-*Z*-didehydrophanylalanine;
N-Trimethylacetyl-4-[(3,5-dichloroisonicotinoyl)amino]-*E*-didehydrophenylalanine;
N-(2-Chloronicotinoyl)-4-[(3,5-dichloroisonicotinoyl)amino]-*Z*-didehydrophenylalanine;
(*Z*)-3-{4-[(3,5-Dichloro-4-pyridinyl)methoxy]phenyl}-2-[(2,6-dimethoxybenzoyl)amino]-2-propenoic acid;
N-(2-Chloronicotinoyl)-4-[(3,5-dichloroisonicotinoyl)amino]-*E*-didehydrophenylalanine;
and the salts, solvates, hydrates and N-oxides thereof.

13. A pharmaceutical composition comprising a compound according to Claim 1 together with one or more pharmaceutically acceptable carriers, excipients or diluents.

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/GB 99/02130

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12 C07D213/81 C07D213/82 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 23 16 881 A (BEECHAM GROUP LTD) 11 October 1973 (1973-10-11) compounds 25 and 26	1,13
A	WO 97 12866 A (ABBOTT LAB) 10 April 1997 (1997-04-10) abstract; claim 1; example 11	1,13
A	WO 93 09795 A (YEDA RES & DEV ;FRIEDMAN MARK M (IL)) 27 May 1993 (1993-05-27) page 6, line 25 - line 34; claim 23	1-13
X,P	WO 99 10312 A (HOFFMANN LA ROCHE) 4 March 1999 (1999-03-04) the whole document	1-13

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 September 1999	04/10/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bosma, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/GB 99/02130

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 710 659 A (TAKEDA CHEMICAL INDUSTRIES LTD) 8 May 1996 (1996-05-08) claim 1; tables 4,5 ---	1
X	EP 0 596 406 A (FUJISAWA PHARMACEUTICAL CO) 11 May 1994 (1994-05-11) preparations ---	1
X	PATENT ABSTRACTS OF JAPAN vol. 006, no. 165 (C-121), 28 August 1982 (1982-08-28) & JP 57 080370 A (KOWA CO), 19 May 1982 (1982-05-19) abstract ---	1
X	JAYNES ET AL: "Synthesis and in vitro antibacterial activity of hygromycin A analogs modified at the C4' aryl position" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 3, no. 8, 1993, pages 1531-1536 6, XP002107045 ISSN: 0960-894X example 9R -----	1

INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/GB 99/02130

Box I Observations wher certain claims were found unsearchable (Continuation f item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: –
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-11 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the examples and to compounds of formula (1), in which Het is a pyridyl group and -Alk1-L1 is a methyloxy- or a carbonylamino group as defined in claim 8.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int tional Application No
PCT/GB 99/02130

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